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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,851	02/01/2006	Jean-Marie Saint-Remy	50304/112001	9175

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
10/27/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/566,851	SAINT-REMY ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46,48-60 and 64-73* is/are pending in the application.

4a) Of the above claim(s) *46 and 48-57* is/are withdrawn from consideration.

5)☒ Claim(s) *58-60,64,65,67,68,70,71 and 73* is/are allowed.

6)☒ Claim(s) *66 and 72* is/are rejected.

7)☒ Claim(s) *69* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/29/09, 7/8/09, and 9/17/09* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received August 12, 2009 are acknowledged.

Claims 1-45, 47, and 61-63 have been canceled.

Claims 49, 58, 64 and 65 have been amended.

Claims 66-73 have been added.

Claims 46, 48-60, and 64-73 are pending in the instant application.

Claims 46 and 48-57 stand withdrawn from consideration as being drawn to a nonelected invention. See 37 CFR 1.142(b) and MPEP § 821.03, for reasons of record set forth in the office action mailed January 25, 2008.

Claims 58-60 and 64-73 are under examination in this office action.

Information Disclosure Statement

2. The IDS forms received 6/29/09, 7/8/09, and 9/17/09 are acknowledged and have been considered.

Specification

3. Applicant's amendment to the title is acknowledged.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The rejection of claims 38 and 40 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement concerning the deposit of named biological materials has been rendered moot by cancellation of said claims as part of the amendments received August 12, 2009.

6. Claims 66 and 72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the antibody of SEQ ID NO:26, an antibody that binds FVIII and comprises the six CDRs of SEQ ID NOs:33-38 wherein the glycosylation site at positions 3 and/or 5 of SEQ ID NO:33 is mutated, an antibody that binds FVIII and comprises SEQ ID NO:4, an antibody that binds FVIII and comprises SEQ ID NO:2, and an antibody that binds FVIII and comprises SEQ ID NO:2 wherein SEQ ID NO:2 is mutated such that position 3 of CDR1 is mutated from N to Q, E, or D or position 5 is mutated from T to A, does not reasonably provide enablement for more. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons of record.

The office action mailed May 18, 2009 states:

> Applicant has claimed a genus of antibodies which comprise "modified" glycosylation in the variable region as compared to a starting antibody which binds and inhibits the activity of factor VIII (a.k.a. an inhibitory antibody). This genus is further characterized in that the affinity of the modified antibody and the starting antibody are "substantially the same". The disclosure on page 22 indicates that to be "substantially the same", the K_D values should differ by less than a factor of 2.5. To support such a genus, applicant has disclosed working examples of antibody derivatives based upon KRIX-1, a known inhibitory antibody that binds FVIII in the C domain. KRIX-1 comprises a glycosylation site (i.e. Asn-Xaa-Ser/Thr) in CDR1 of the heavy chain, and the derivatives comprise mutations such that the Asn is replaced with Gln, Asp, Glu, or Ala. These derivatives are identified as Krix-1Q, Krix-1D, Krix-1E, and Krix-1A respectively.
>
> The breadth of the independent claim reads on antibodies which comprise modified glycosylation, yet the staring antibody that is modified is not identified other than that it is an inhibitory antibody that binds FVIII. Note that while the working examples deal with the removal of glycosylation from Krix-1 via mutagenesis, the claims also read upon the introduction of a glycosylation site in the variable domain.
>
> It is well established in the art that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (Janeway et al., see entire selection). It is also known that single amino acid changes in a CDR can abrogate the antigen binding function of an antibody (Rudikoff et al., see entire document, particularly the abstract and the middle of the left column of page 1982).
>
> It is also known that given one specified variable domain, either heavy or light, that skilled artisans can screen libraries to identify other variable domains that will pair with the starting variable domain and maintain antigen specificity (Portolano et al., see entire document, particularly figure 1). Thus, it is known in the art that artisans can screen for other variable domains that will ensure a functional antibody of defined antigen specificity if a full variable domain (heavy or light) is used in the screening assay.

Glycosylation within variable domains of antibodies is known in the art, yet the results of either introducing or removing such glycosylation upon antigen binding is not predictable. Indeed, introduction as well as removal of glycosylation in a CDR can either increase or decreased affinity for the cognate antigen, with the position where the N-glycan is attached as well as the structure of the antigen and starting antibody influencing observed properties in unpredictable ways (see particularly Wright et al., Endo et al., and US patent 5,714,350). Typically, reported changes in affinity are more than 3 fold. However, the specification indicates on pages 20-21 that the inventors' observations are unexpected because it has not been previously reported that glycosylation can modulate the function of an antibody other than by altering the antibody's affinity or specificity. Given the unexpected nature of applicant's observations, as well as the teachings of unpredictability in the art, a skilled artisan would not reasonably expect that use of a staring inhibitory antibody other than Krix-1, or the introduction of another glycosylation site into the variable domain of Krix-1 would generate an antibody that differs by less than a factor of 2.5 in its affinity for binding FVIII.

Since all CDRs contribute to binding, and binding can be disrupted in unpredictable ways due to mutations as small as a single point mutation, applicant's claimed genus of antibodies which recite "percent identity" or "sequence similarity" are not reasonably enabled because they read on mutations which can occur with the CDRs of the variable domain. As evidenced by the enclosed sequence alignment, antibody sequences that are more than 90% similar can be found in the databases that are specific for antigens other than FVIII, indicating that additional structural information is needed to ensure maintenance of antigen specificity. Note that the working examples have designated two positions in CDR1 of the heavy chain which can be mutated (i.e. 3 or 5) yet claims such as 64 recite that the mutation can occur at positions 3, 4, or 5. Note also that in order to perform any sort of screening assay to identify other antibody chains (either heavy or light) a specifically defined antibody chain of a single sequence is needed to perform the screening assay as per Portolano et al. Thus, a claim such as 42 is not reasonably enabled because it allows for two variables (i.e. the heavy chain comprises unknown mutations and the light chain can be anything) yet screening assays used to identify such antibodies require one of the variables to be a constant.

Therefore, based upon the breadth of the claimed invention, the teachings of the art, and the amount of guidance and direction disclosed in the specification, a skilled artisan would be unable to make and use the full breadth of the claimed genus of antibodies without first performing additional, unpredictable research.

Applicant's arguments filed August 18, 2009 have been fully considered but they are not persuasive. Applicant has argued that the claims as amended as well as the newly presented claims recite the antibody structural requirements needed to support a finding of enablement as set forth in the prior office action.

This argument is not persuasive. Specifically, the prior office action indicated that an antibody that binds a specifically identified antigen can minimally be defined by either a recitation of all six CDR sequences or by recitation of a full length variable domain (either heavy or light). In independent claim 66, the claimed antibody is recited as binding factor VIII, yet only the three CDRs of the heavy chain are recited. As explained in the office action of record, three CDRs without identification of specific framework sequences (such that the artisan would have the complete sequence of a

variable domain) is insufficient structural information to allow a skilled artisan to make and use the claimed invention without performing additional unpredictable research. Note that SEQ ID NO:26 is a singe chain Fv antibody and thus it comprises full length V_H and V_L domains, and is therefore fully enabled.

Claim Objections

7. Claim 69 is objected to as being dependent upon a rejected independent claim, but would be allowable if rewritten in independent form including all of the limitations of the independent claim and any intervening claims.

8. Claims 58-60, 64, 65, 67, 68, 70, 71, and 73 are allowable.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Primary Examiner
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